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(54) **PROCESS FOR PREPARING BOSENTAN**

VERFAHREN ZUR HERSTELLUNG VON BOSENTAN

PROCÉDÉ DE PRÉPARATION DE BOSENTAN

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(56) References cited:
EP-A- 0 526 708 **EP-A- 0 743 307**
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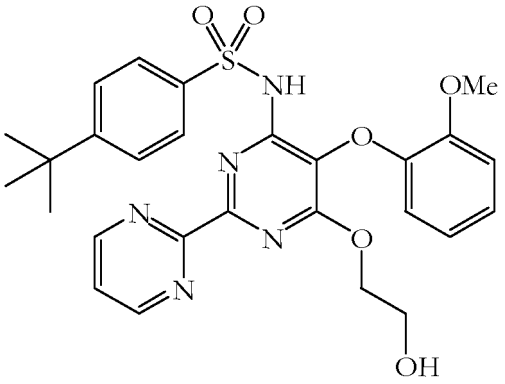
Description

Field of the invention

[0001] The present invention relates to a novel intermediate useful in the preparation of bosentan and to processes for the preparation of said intermediate and bosentan.

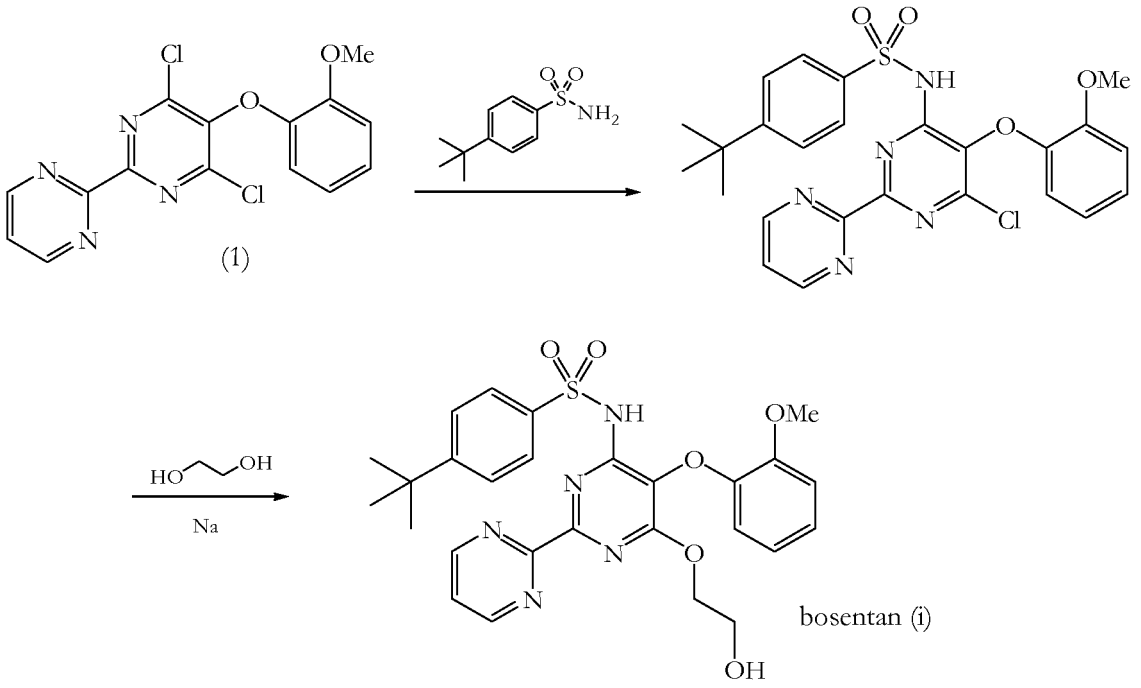
Background of the invention

[0002] Bosentan, represented by structural formula (i) and chemically named 4-tert-butyl-*N*-[6-(2-hydroxyethoxy)-5-(2-methoxyphenoxy)-2-(2-pyrimidinyl)-pyrimidin-4-yl]-benzenesulfonamide is an endothelin receptor antagonist. It is used for the treatment of disorders which are associated with endothelin activities, in particular circulatory and cardiovascular disorders such as hypertension, ischemia, pulmonary hypertension, vasospasm and angina pectoris. The marketed product comprising bosentan, Tracleer®, is indicated for the treatment of pulmonary arterial hypertension (PAH) to improve exercise capacity and symptoms in patients with grade III functional status.



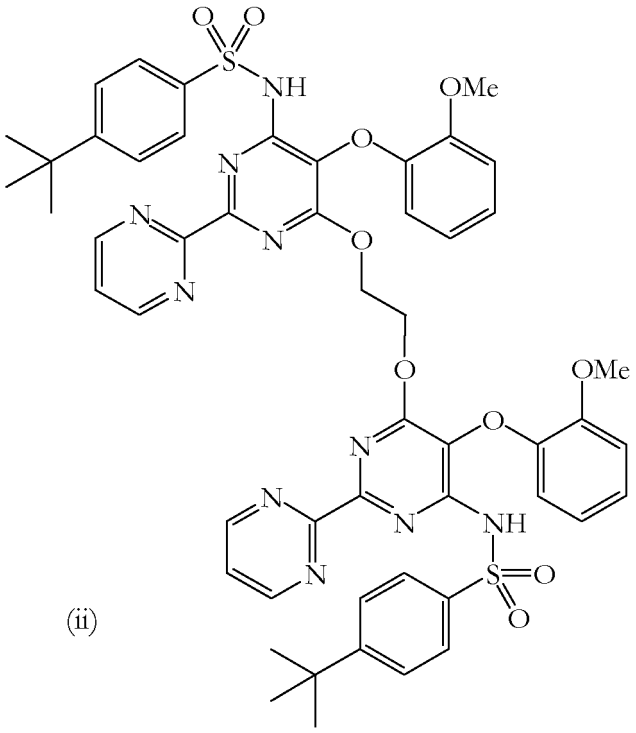
(i)

[0003] Bosentan was first described in US 5292740. The preparation method involves two steps (as shown in Scheme 1) starting from the dichloro compound, 4,6-dichloro-5-(o-methoxyphenoxy)-2,2'-bipyrimidine (1). The second reaction step is carried out in ethylene glycol with sodium metal used as the base at a temperature of 100-110°C.



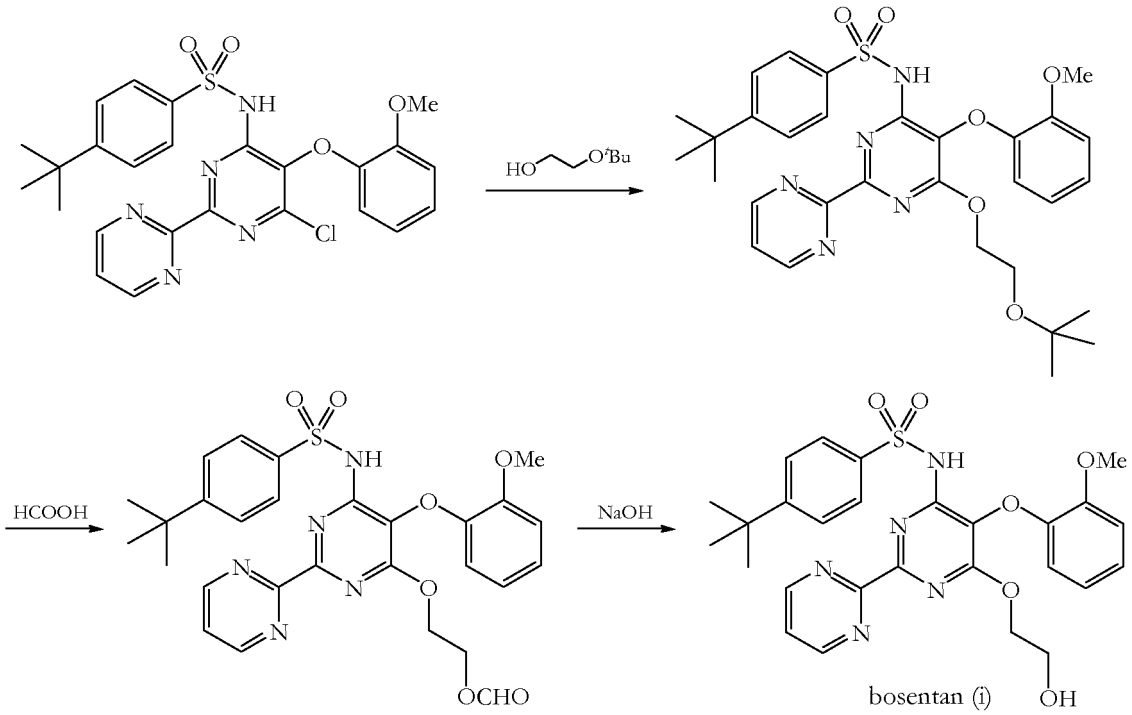
Scheme 1

[0004] One of the disadvantages of this process is the formation of an undesired ethylene glycol bis-sulfonamide dimer having formula (ii) in which two molecules of the pyrimidine monohalide molecule are coupled with one molecule of ethylene glycol. The removal of this impurity requires costly and laborious separation steps. To minimize the formation of this impurity a large excess of ethylene glycol is used. However, using a large excess of ethylene glycol is impractical on a large industrial scale, because ethylene glycol is toxic and its high boiling point means that its removal by distillation is energy and time consuming.



[0005] Many other processes have been disclosed for the preparation of bosentan, however, they are all multistep processes requiring cumbersome purification processes to obtain the pure product.

[0006] US 6136971 discloses a process (as shown in Scheme 2) for the preparation of bosentan with high HPLC purity (99.1%) and solves the problem of the dimer formation by utilising a mono-protected 1,2-diheteroethylene anion. In a particularly preferred aspect of the disclosed invention the protecting group is a tert-butyl group used to protect one hydroxyl group of ethylene glycol as an ether. The protecting group is then removed with formic acid to produce a formyloxy-protected ethylene glycol sulfonamide derivative. Treatment of this compound with a base, preferably sodium hydroxide, then produces an ethylene glycol sulfonamide derivative containing a free hydroxy group, namely bosentan.



Scheme 2

[0007] In view of the above disadvantages associated with the prior art there is a need for an improved process for the preparation of bosentan which is economical and high yielding and which provides bosentan with a high degree of purity.

Summary of the invention

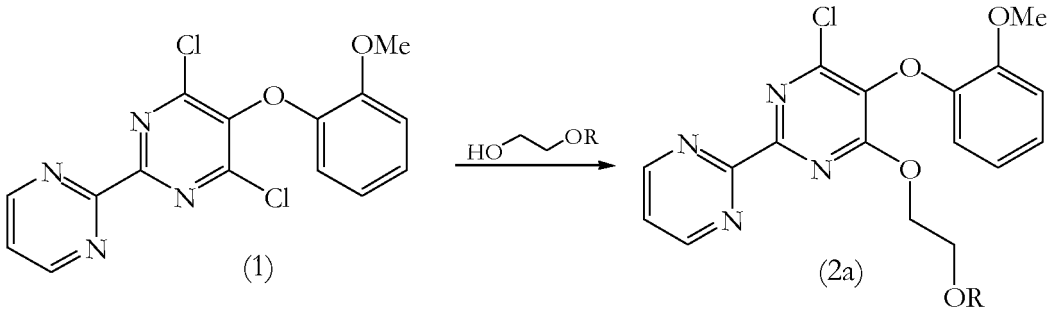
[0008] The present inventors have found that coupling of a dichloro compound, 4,6-dichloro-5-(2-methoxyphenoxy)-2,2'-bipyrimidine (1), with a mono-protected ethylene glycol of formula $HOCH_2CH_2OR$, wherein R is a hydroxyl protecting moiety, followed by introduction of a sulfonamide group in the next step provides an improved process for the preparation of bosentan with a very high purity. This process has the unique and surprising advantage of requiring less sulfonamide than prior art processes, which is an expensive raw material compared to the ethylene glycol derivative.

Detailed description of the invention

[0009] The present invention provides an efficient and economical synthesis of bosentan, which is high yielding and affords the product with very high purity on a commercial scale.

[0010] The present inventors have found that coupling the dichloro compound (1) with the mono-protected ethylene glycol component first and then introducing the sulfonamide moiety in a second step as opposed to the prior art processes where the sulfonamide moiety is coupled to the dichloro compound (1) first and the mono-protected ethylene glycol is added in a second step, provides a process with a number of surprising advantages. In particular the process, which further provides a novel intermediate having formula (2a) according to the invention, results in bosentan having a purity of more than 99.70%, preferably greater than 99.8%, and most preferably more than 99.9%. Such purity levels have not

been seen before in the prior art.



[0011] Accordingly, a first aspect according to the invention provides an improved process for the preparation of bosentan utilizing a compound of formula (2a). In one embodiment according to the invention the process comprises the steps of:

(a) adding a dichloro compound of formula (1) to a mono-protected ethylene glycol of formula $HOCH_2CH_2OR$, wherein R is a hydroxyl protecting moiety, resulting in a reaction mixture comprising a compound of formula (2a);
(b) coupling compound (2a) with 4-tert-butyl phenyl sulfonamide;
(c) removing the protecting moiety R; and
(d) isolating bosentan from the mixture obtained in step (c).

[0012] In a particularly preferred embodiment R is stable in basic and mildly acidic conditions. Of course the skilled person will realize that there are a number of further groups that may serve as protecting moieties on the ethylene glycol, indeed any hydroxyl protecting groups that are stable under basic and mildly acidic conditions will be suitable for use in the working of the invention. Examples of said protecting groups can be found in T.W. Greene & P.G.M. Wuts, Protective Groups in Organic Synthesis (3rd ed., John Wiley & Sons, 1999). Accordingly, particularly preferred R groups may be selected from the group comprising alkyl, aryl, arylalkyl, allyl, silyl, benzoate and pivalate moieties. In a particularly preferred embodiment R is tert-butyl.

[0013] A preferred reaction temperature for this coupling of the mono-protected ethylene glycol and the 4,6-dichloro-5-(2-methoxyphenoxy)-2,2'-bipyrimidine (1) is from about 15°C to about 90°C, more preferably from about 30°C to about 90°C, and most preferably from about 50°C to about 60°C. A preferred reaction time is about 1-10 hours, more preferably about 1-5 hours, and most preferably about 1-3 hours. Preferably from about 1 equivalents (eq) to about 10 equivalents (eq) of mono-protected ethylene glycol relative to 4,6-dichloro-5-(2-methoxyphenoxy)-2,2'-bipyrimidine (1) are used, more preferably about 1 eq to about 5 eq, and most preferably about 3 eq. In particularly preferred embodiments, the mono-protected ethylene glycol is reacted with the 4,6-dichloro-5-(2-methoxyphenoxy)-2,2'-bipyrimidine (1) in the presence of a base. Preferably the base is selected from the group comprising alkali metal hydroxides (such as lithium and sodium hydroxide), alkaline earth metal hydroxides, sodium metal, DBU, DBN, dimethylaminopyridine (DMAP), and pyridine. Most preferably the base is an alkali metal hydroxide and a particularly preferred base is sodium hydroxide. Preferably, the reaction is carried out in an organic solvent, which is preferably toluene but alternative solvents can be selected from the group comprising toluene, xylene, dimethyl sulfoxide (DMSO), tetrahydrofuran (THF), acetonitrile, dimethylformamide (DMF) and dimethylacetamide.

[0014] In step (b), compound (2a) is coupled with 4-tert-butyl phenyl sulfonamide. Preferably about 1 eq to about 2 eq of 4-tert-butyl phenyl sulfonamide relative to compound (2a) are used, preferably about 1 eq. Preferably the reaction is carried out in the presence of a base, such as potassium carbonate. A preferred reaction temperature is from about 100°C to about 150°C, preferably about 120°C. A preferred reaction time is about 8-15 hours, preferably about 10 hours. Preferably the reaction is carried out in an organic solvent, such as DMSO.

[0015] In a further embodiment the ethylene glycol protecting moiety can be removed by any means known in the art. For example the inventors have found that acidification followed by treatment with a base is particularly efficient at removing the protecting group. Particularly preferred removal conditions involve treatment with formic acid followed by treatment with sodium hydroxide, particularly in the preferred embodiment wherein the protecting group is a tert-butyl ether moiety.

[0016] In another preferred embodiment the bosentan is isolated in step (d) by filtration and dried under reduced pressure until a constant weight is achieved.

[0017] The process according to the first aspect of the present invention is preferably carried out on an industrial scale, preferably providing bosentan in batches of about 500g, 1kg, 2kg, 5kg, 10kg, 50kg, 100kg or more.

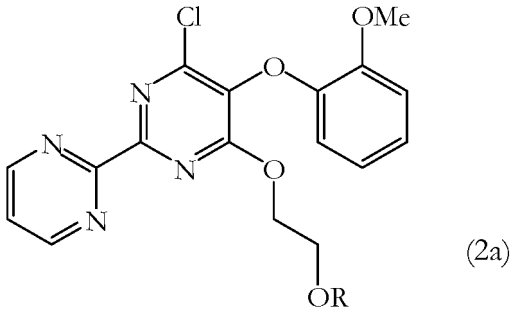
[0018] The process according to the first aspect of the present invention preferably provides bosentan in a molar yield

of 30%, 40%, 50%, 60% or more from the dichloro compound of formula (1).

[0019] The process according to the first aspect of the present invention is preferably carried out without the use of chromatography.

[0020] The bosentan obtained by the process according to the first aspect of the present invention preferably has an HPLC purity of 97% or more, preferably 98% or more, preferably 99% or more, preferably 99.3% or more, preferably 99.5% or more, preferably 99.7% or more, preferably 99.8% or more, preferably 99.9% or more. Preferably the bosentan comprises less than about 0.1%, preferably less than about 0.05% of the dimer impurity (ii) (as measured by HPLC).

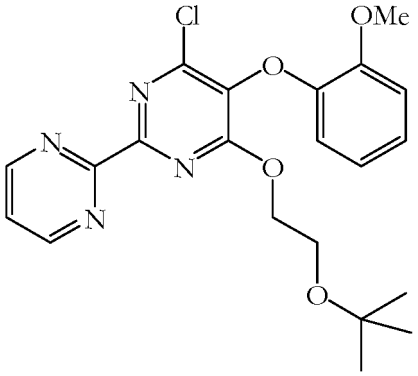
[0021] According to a second aspect of the invention, there is provided a novel compound of formula (2a) or salts or crystalline forms thereof:



(2a)

,

wherein R is a hydroxyl protecting moiety selected from the group comprising alkyl, alkenyl, alkynyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, alkylaryl, alkenylaryl, alkynylaryl, allyl, silyl, benzoate and pivalate moieties. Preferably R is tert-butyl, providing a compound having structure (2):



(2)

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[0022] It has been found that this compound is useful in the preparation of certain sulfonamide compounds, in particular bosentan. Of course it will be evident to the skilled person that different forms of the novel intermediate may be utilised in the working of the invention. They may comprise salt forms, different crystalline forms or amorphous forms, or isomers. The inventors have found that salts selected from the following group are particularly useful, said group comprising: a tartrate, succinate, oxalate, pimelate, adipate, acetate, suberate, salicylate, mesylate, malate, malonate, maleate, camphorsulfonate, mandelate, hydrochloride, hydrogen sulfate, sulfate, hydrobromide, besylate, benzoate, dihydrogen phosphate, glutarate, or citrate salt. Again it will be understood that the salts may be prepared by any means known in the art, in particular by reaction with the corresponding acid.

[0023] In a third aspect according to the invention there is provided a process for the preparation of a compound of formula (2a) comprising coupling a dichloro compound of formula (1) to a mono-protected ethylene glycol having formula $HOCH_2CH_2OR$, wherein R is as previously described. Preferably R is stable in basic and mildly acidic conditions, particularly preferred is wherein R may be selected from the group comprising alkyl, aryl, arylalkyl, allyl, silyl, benzoate and pivalate moieties, but most preferably R is tert-butyl. The skilled person will be aware that there are a number of further groups that may serve as protecting moieties on the ethylene glycol as previously described in relation to the first aspect of the present invention.

[0024] A preferred reaction temperature for this coupling is from about 15°C to about 90°C, more preferably from about 30°C to about 90°C, and most preferably from about 50°C to about 60°C. A preferred reaction time is about 1-10 hours, more preferably about 1-5 hours, and most preferably about 1-3 hours. Preferably from about 1 equivalents (eq) to about

10 equivalents (eq) of mono-protected ethylene glycol relative to the dichloro compound of formula (1) are used, more preferably about 1 eq to about 5 eq, and most preferably about 3 eq. In particularly preferred embodiments, the mono-protected ethylene glycol is reacted with the 4,6-dichloro-5-(2-methoxyphenoxy)-2,2'-bipyrimidine (1) in the presence of a base. Preferably the base is selected from the group comprising alkali metal hydroxides (such as lithium and sodium hydroxide), alkaline earth metal hydroxides, sodium metal, DBU, DBN, DMAP, and pyridine. Most preferably the base is an alkali metal hydroxide and a particularly preferred base is sodium hydroxide. Preferably, the reaction is carried out in an organic solvent, which is preferably toluene but alternative solvents can be selected from the group comprising toluene, xylene, dimethyl sulfoxide (DMSO), tetrahydrofuran (THF), acetonitrile, dimethylformamide (DMF) and dimethylacetamide.

[0025] Preparing the mono-protected ethylene glycol pyrimidine derivative of formula (2a) or (2) using a mono-protected ethylene glycol derivative prevents formation of the undesired ethylene glycol bis-sulfonamide compound of formula (ii). Without being bound by any theory, it is believed that in some processes described in the prior art such as for example US 5292740, the hydroxy group of some of the initially formed ethylene glycol derivative reacts with unreacted sodium ethylene glycol ($NaOCH_2CH_2OH$) or other bases which may be present in the reaction mixture to form an anion which then reacts with another molecule of pyrimidine mono-halide to produce the undesired ethylene glycol bis-sulfonamide derivative. By using the mono-protected ethylene glycol pyrimidine derivative (2a) or (2), the present invention eliminates any possibility of forming such an anion, thus completely eliminating production of the undesired ethylene glycol bis-sulfonamide derivative. This elimination of the production of the undesired ethylene glycol bis-sulfonamide derivative results in a higher overall product yield and easier product purification.

[0026] The process according to the third aspect of the present invention is preferably carried out on an industrial scale, preferably providing compound (2a) in batches of about 500g, 1kg, 2kg, 5kg, 10kg, 50kg, 100kg or more.

[0027] The process according to the third aspect of the present invention preferably provides compound (2a) in a molar yield of 80%, 85%, 90% or more from the dichloro compound of formula (1).

[0028] The process according to the third aspect of the present invention is preferably carried out at a temperature of 90°C, 80°C, 70°C, 60°C or less.

[0029] The process according to the third aspect of the present invention is preferably carried out without the use of chromatography.

[0030] In all of the aspects of the present invention described above, R is a hydroxyl protecting moiety. Preferably R is selected from the group comprising alkyl, alkenyl, alkynyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, alkylaryl, alkenylaryl, alkynylaryl, allyl, silyl, benzoate and pivalate moieties. Preferably R is selected from the group comprising alkyl, aryl, arylalkyl, allyl, silyl, benzoate and pivalate moieties.

[0031] Alkyl, alkenyl and alkynyl moieties preferably comprise 1 to 12 carbon atoms, preferably 1 to 8 carbon atoms, preferably 1 to 6 carbon atoms, preferably 1 to 4 carbon atoms. A preferred alkyl moiety is tert-butyl.

[0032] Preferably an aryl moiety comprises 4 to 14 carbon atoms, preferably 6 to 10 carbon atoms. A typical aryl moiety is phenyl.

[0033] Arylalkyl, arylalkenyl, arylalkynyl, alkylaryl, alkenylaryl and alkynylaryl moieties preferably comprise 5 to 20 carbon atoms, preferably 7 to 15 carbon atoms. A typical arylalkyl moiety is benzyl.

Preferably an allyl moiety is a $-CH_2-CH=CH-R'$ group, wherein R' is hydrogen or an alkyl, alkenyl, alkynyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, alkylaryl, alkenylaryl or alkynylaryl group. Preferably R' is hydrogen.

Preferably a silyl moiety is a $-SiR'_3$ group, wherein R' is independently selected from hydrogen or an alkyl, alkenyl, alkynyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, alkylaryl, alkenylaryl or alkynylaryl group. Typical silyl moieties are trimethylsilyl (TMS), triethylsilyl, triisopropylsilyl, dimethylisopropylsilyl, diethylisopropylsilyl, dimethyl-t-hexylsilyl, t-butyldimethylsilyl (TBDMS), t-butyldiphenylsilyl (TBDPS), tribenzylsilyl, tri-p-xylylsilyl, triphenylsilyl (TPS), diphenylmethylsilyl (DPMS), and t-butylmethoxyphenylsilyl (TBMPS).

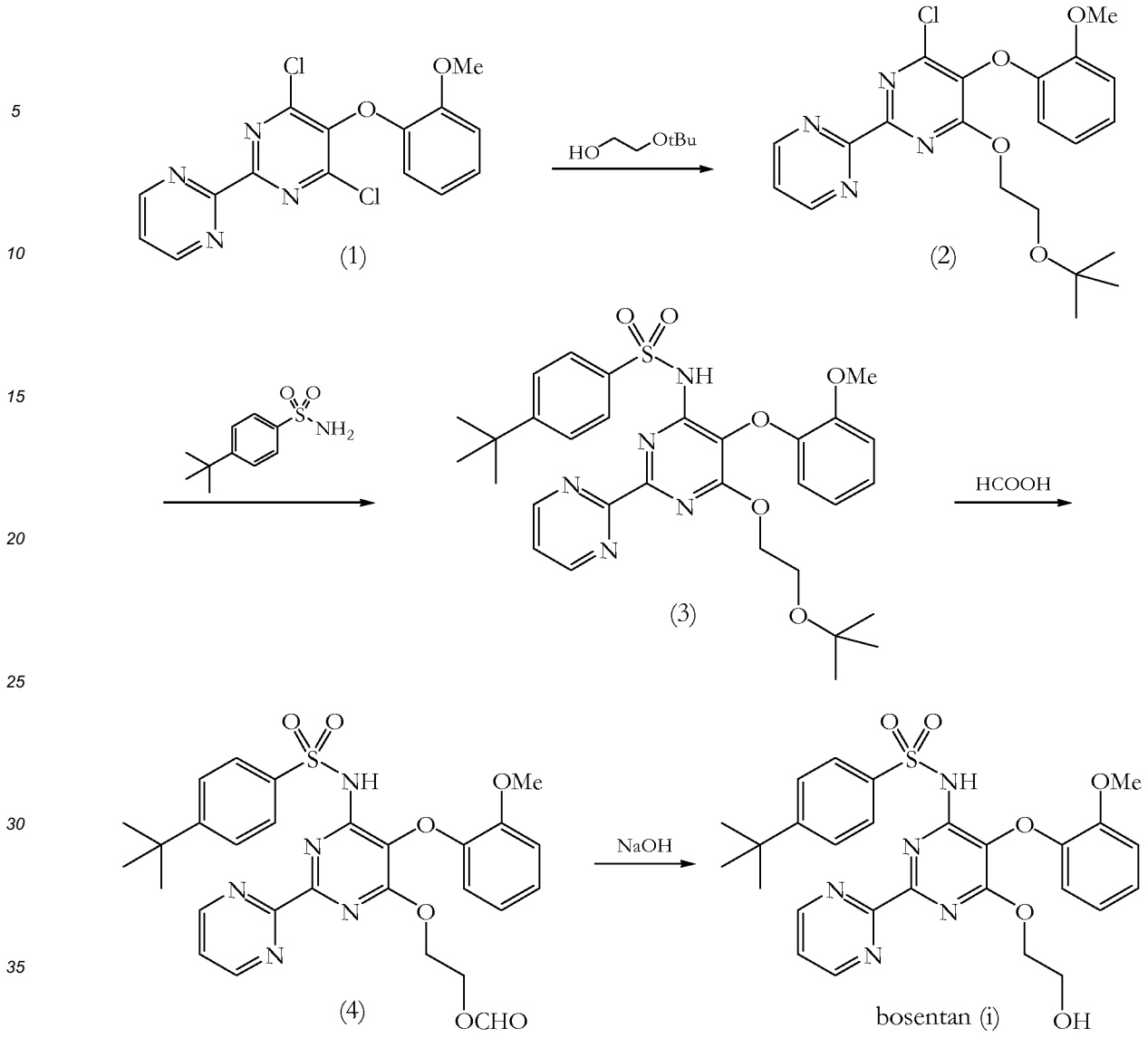
[0034] Bosentan prepared by a process according to the invention may be used to provide a pharmaceutical composition. Preferably the composition is a solid composition, most preferably a tablet or capsule composition.

[0035] The details of the invention, its objects and advantages are explained hereunder in greater detail in relation to exemplary illustrations.

Examples

Preparation of bosentan

[0036] A process according to the invention is represented below as a schematic diagram. The compound number descriptors refer to the numbered compounds in the schematic diagram.



Process for conversion of compound (1) to (2) (stage 1)

[0037] Sodium hydroxide (1 eq) was added to ethylene glycol mono tert-butyl ether (3 eq) in toluene (7 vol). Compound (1) (1 eq) was added and the reaction mixture heated at 55°C for 2 hours. After completion of the reaction, the mixture was acidified with a 1:1 mixture of concentrated HCl and water (0.4 vol) to pH 2. The organic layer was separated and washed with water (5 vol). The toluene was distilled off at 40°C under vacuum (10mbar) and the product (compound (2)) was obtained as a light brown solid (molar yield = 90%).

Process for conversion of compound (2) to 3 (stage 2)

[0038] A mixture of DMSO, (10 vol), potassium carbonate (1.2 eq), 4-tert-butyl phenyl sulfonamide (1 eq) and compound (2) (1 eq) was heated at 120°C for 10 hours. After completion of the reaction, water (25 vol) was added to the reaction mixture, the reaction mixture was acidified with a solution of tartaric acid (1.8 eq) in water (25 vol) to pH 3, and the precipitated solid was filtered under vacuum and dried under vacuum (10mbar) at 50°C for 2 hours. The product (compound (3)) was obtained as a light brown solid (molar yield = 100%).

Process for conversion of compound (3) to (4) (stage 3)

[0039] Compound (3) (1 eq) in formic acid (2 vol) was heated at 85°C for 4 hours. Toluene (8.3 vol) was added to the reaction mixture and the formic acid distilled out azeotropically using toluene under vacuum (10mbar) at 50°C. The

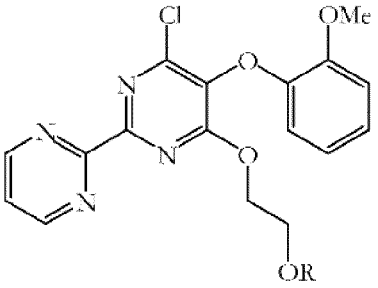
brown thick oil obtained was taken in ethanol (3.3 vol) and heated to reflux. The clear solution was cooled to 25-30°C, stirred for 3 hours and the resultant solid filtered. The wet solid was mixed with ethanol (1.6 vol), heated to reflux and cooled to 25-30°C. The resultant solid (compound (4)) was then filtered (molar yield = 47%).

Process for conversion of compound (4) to bosentan (i) (stage 4)

[0040] Compound (4) (1 eq) was taken in ethanol (2.5 vol) and added to a solution of sodium hydroxide (3 eq) in water (2 vol). Water (6 vol) was added to the clear solution and stirred at 25-30°C for 1 hour. The reaction mixture was acidified with concentrated HCl (0.33 vol) to pH 5.5, water (10 vol) was added, and the mixture stirred for 1 hour and filtered. A white solid was obtained which was dried under vacuum for 4 hours. The resultant bosentan had a HPLC purity = 99.71% (molar yield = 93%).

Claims

1. A process for preparing bosentan utilizing a compound of formula (2a):



(2a)

,

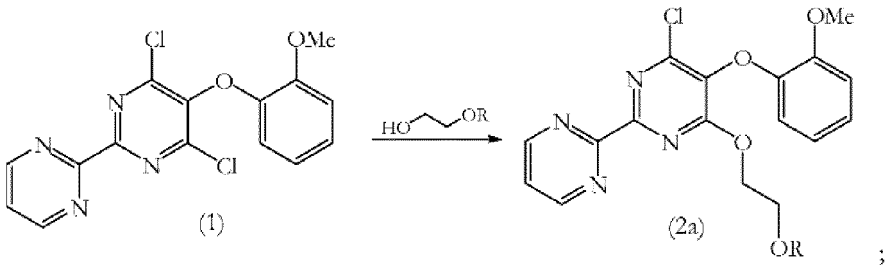
wherein R is a hydroxyl protecting moiety.

2. A process according to claim 1, wherein R is:

(i) stable in basic and mildly acidic conditions; and/or
(ii) selected from the group comprising alkyl, aryl, arylalkyl, allyl, silyl, benzoate and pivalate moieties; and/or
(iii) tert-butyl.

3. A process for preparing bosentan comprising:

(a) reacting a dichloro compound of formula (1) with a mono-protected ethylene glycol of formula $HOCH_2CH_2OR$, wherein R is a hydroxyl protecting moiety, to afford a compound of formula (2a):



;

(b) coupling compound (2a) with 4-tert-butyl phenyl sulfonamide;
(c) removing the protecting moiety R; and
(d) isolating bosentan from the mixture obtained in step (c).

4. A process according to claim 3, wherein R is:

(i) stable in basic and mildly acidic conditions; and/or

(ii) selected from the group comprising alkyl, aryl, arylalkyl, allyl, silyl, benzoate and pivalate moieties; and/or
(iii) tert-butyl; and/or
(iv) tert-butyl, and wherein the tert-butyl group is removed by treatment with formic acid followed by treatment with sodium hydroxide.

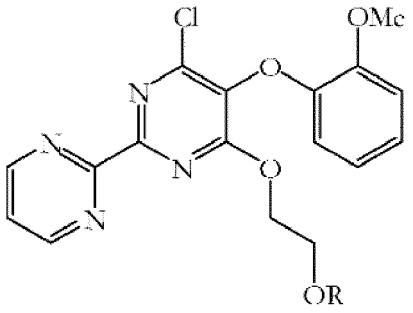
5. A process according to claim 3 or 4, wherein in step (a) the dichloro compound of formula (1) and the mono-protected ethylene glycol are reacted in the presence of:

(i) a base; and/or
(ii) a base selected from the group comprising alkali metal hydroxides, alkaline earth metal hydroxides, sodium metal, DBU, DBN, DMAP and pyridine; and/or
(iii) an alkali metal hydroxide; and/or
(iv) lithium or sodium hydroxide; and/or
(v) sodium hydroxide.

6. A process according to any one of claims 3-5, wherein:

(i) the process is carried out in an organic solvent; and /or
(ii) step (a) is carried out in an organic solvent selected from the group comprising toluene, THF, xylene, DMF, DMSO, acetonitrile and dimethylacetamide; and/or
(iii) step (a) is carried out in toluene; and/or
(iv) the reaction mixture in step (a) is heated to between about 30-90°C; and/or
(v) the reaction mixture in step (a) is heated to between about 50-60°C; and/or
(vi) the bosentan is isolated in step (d) by filtration and then dried under reduced pressure until a constant weight is achieved.

7. A compound having the structure as shown in formula (2a) or a salt or crystalline form thereof:



(2a)

,

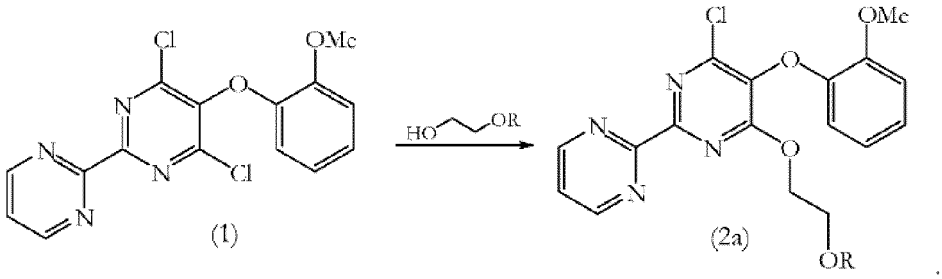
wherein R is a hydroxyl protecting moiety selected from the group comprising alkyl, alkenyl, alkynyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, alkylaryl, alkenylaryl, alkynylaryl, allyl, silyl, benzoate and pivalate moieties.

8. A compound according to claim 7, wherein R is:

(i) selected from the group comprising alkyl, aryl, arylalkyl, allyl, silyl, benzoate and pivalate moieties; and/or
(ii) tert-butyl.

9. A compound according to claims 7 or 8, wherein the salt is selected from the group comprising: a tartrate, succinate, oxalate, pimelate, adipate, acetate, suberate, salicylate, mesylate, malate, malonate, maleate, camphorsulfonate, mandelate, hydrochloride, hydrogen sulfate, sulfate, hydrobromide, besylate, benzoate, dihydrogen phosphate, glutarate, or citrate salt.

10. A process for preparing a compound of formula (2a) comprising coupling a dichloro compound of formula (1) to a mono-protected ethylene glycol of formula $HOCH_2CH_2OR$, wherein R is a hydroxyl protecting moiety, to afford a compound of formula (2a):



11. A process according to claim 10, wherein R is

(i) stable in basic and mildly acidic conditions; and/or
(ii) selected from the group comprising alkyl, aryl, arylalkyl, allyl, silyl, benzoate and pivalate moieties; and/or
(iii) tert-butyl.

12. A process according to claim 10 or 11, wherein the dichloro compound of formula (1) is coupled to the mono-protected ethylene glycol in the presence of:

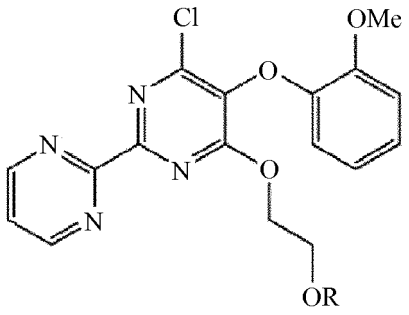
(i) a base; and/or
(ii) a base selected from the group comprising alkali metal hydroxides, alkaline earth metal hydroxides, sodium metal, DBU, DBN, DMAP and pyridine; and/or
(iii) an alkali metal hydroxide; and/or
(iv) lithium or sodium hydroxide; and/or
(v) an organic solvent; and/or
(vi) an organic solvent selected from the group comprising toluene, THF, xylene, DMF, DMSO, acetonitrile and dimethylacetamide; and/or
(vii) toluene.

13. A process according to any one of claims 10-12, wherein the reaction mixture is heated to :

(i) between about 30-90°C; and/or
(ii) between about 50-60°C.

Patentansprüche

1. Ein Verfahren zur Herstellung von Bosentan unter Verwendung einer Verbindung der Formel (2a):



(2a)

wo inrR ein Hydroxyl-schützender Teil ist.

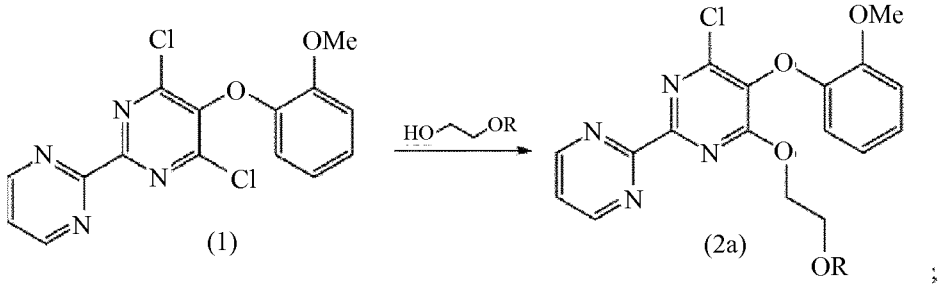
2. Ein Verfahren gemäß Anspruch 1, worin R Folgendes ist:

(i) stabil unter basischen und leicht sauren Bedingungen; und/oder
(ii) ausgewählt aus der Gruppe, die besteht aus Alkyl-, Aryl-, Arylalkyl-, Allyl-, Silyl-, Benzoat- und Pivalat-Teilen; und/oder

(iii) tert-Butyl.

3. Ein Verfahren zur Herstellung von Bosentan, das Folgendes umfasst:

(a) Reaktion einer Dichlor-Verbindung der Formel (1) mit einem mono-geschützten Ethylenglykol der Verbindung $HOCH_2CH_2OR$, worin R ein Hydroxyl-schützender Teil ist, um eine Verbindung der Formel (2a) zu erhalten:



;

(b) Kopplung der Verbindung (2a) mit 4-tert-Butylphenylsulfonamid;
(c) Entfernung des schützenden Teils R; und
(d) Isolierung von Bosentan aus der in Schritt (c) gewonnenen Mischung.

4. Ein Verfahren gemäß Anspruch 3, worin R Folgendes ist:

(i) stabil unter basischen und leicht sauren Bedingungen; und/oder
(ii) ausgewählt aus der Gruppe, die besteht aus Alkyl-, Aryl-, Arylalkyl-, Allyl-, Silyl-, Benzoat- und Pivalat-Teilen; und/oder
(iii) tert-Butyl; und/oder
(iv) tert-Butyl, und worin die tert-Butyl-Gruppe durch Behandlung mit Methansäure und anschließender Behandlung mit Natriumhydroxid entfernt wird.

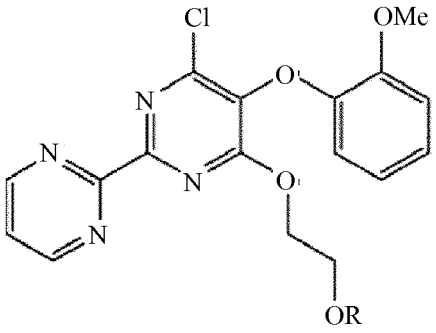
5. Ein Verfahren gemäß Anspruch 3 oder 4, worin in Schritt (a) die Dichlor-Verbindung von Formel (1) und das mono-geschützte Ethylenglykol in Reaktion gebracht werden in Gegenwart:

(i) einer Base; und/oder
(ii) einer Base, die aus der Gruppe ausgewählt wird, die besteht aus Alkalimetallhydroxiden, Erdalkalimetallhydroxiden, Natrium-Metallen, DBU, DBN, DMAP und Pyridin; und oder
(iii) eines Alkalimetallhydroxids; und/oder
(iv) von Lithium- oder Natriumhydroxid; und/oder
(v) von Natriumhydroxid.

6. Ein Verfahren gemäß eines der Ansprüche 3-5, worin:

(i) das Verfahren in einem organischen Lösungsmittel ausgeführt wird; und/oder
(ii) Schritt (a) in einem organischen Lösungsmittel ausgeführt wird, das aus der Gruppe ausgewählt wird, die besteht aus Toluen, THF, Xylen, DMF, DMSO, Acetonitril und Dimethylacetamid; und/oder
(iii) Schritt (a) in Toluen ausgeführt wird; und/oder
(iv) das Reaktionsgemisch in Schritt (a) auf eine Temperatur von ca. 30-90 °C erhitzt wird; und/oder
(v) das Reaktionsgemisch in Schritt (a) auf eine Temperatur von ca. 50-60 °C erhitzt wird; und/oder
(vi) das Bosentan in Schritt (d) durch Filtration isoliert und dann unter reduziertem Druck getrocknet wird, bis eine Gewichtskonstanz erzielt wird.

7. Eine Verbindung, welche die in Formel (2a) dargestellte Struktur aufweist, oder ein Salz oder eine kristalline Form dieser:



(2a)

,

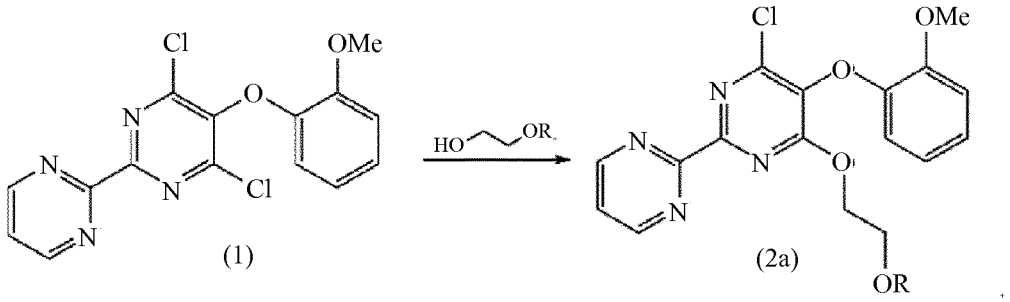
worin R ein Hydroxyl-schützender Teil ist, der aus der Gruppe ausgewählt wird, die besteht aus Alkyl-, Alkenyl-, Alkynyl-, Aryl-, Arylalkyl-, Arylalkenyl-, Arylalkynyl-, Alkylaryl-, Alkenylaryl-, Alkynylaryl-, Allyl-, Silyl-, Benzoat- und Pivalat-Teilen.

8. Eine Verbindung gemäß Anspruch 7, worin R Folgendes ist:

(i) ausgewählt aus der Gruppe, die besteht aus Alkyl-, Aryl-, Arylalkyl-, Allyl-, Silyl-, Benzoat- und Pivalat-Teilen; und/oder
(ii) tert-Butyl.

9. Eine Verbindung gemäß Ansprüchen 7 oder 8, worin das Salz aus der Gruppe ausgewählt wird, die besteht aus: Tartrat, Succinat, Oxalat, Pimelat, Adipat, Acetat, Suberat, Salicylat, Mesylat, Malat, Malonat, Maleat, Camphorsulfonate, Mandelat, Hydrochlorid, Hydrogensulfat, Sulfat, Hydrobromid, Besylat, Benzoat, Dihydrogenphosphat, Glutarat oder Citrat.

10. Ein Verfahren zur Herstellung einer Verbindung der Formel (2a), das die Kopplung einer Dichlor-Verbindung der Formel (1) mit einem mono-geschützten Ethylenglykol der Formel $HOCH_2CH_2OR$ umfasst, worin R ein Hydroxyl-schützender Teil ist, um eine Verbindung der Formel (2a) zu erhalten:



(1) (2a)

11. Ein Verfahren gemäß Anspruch 10, worin R Folgendes ist:

(i) stabil unter basischen und leicht sauren Bedingungen; und/oder
(ii) ausgewählt aus der Gruppe, die besteht aus Alkyl-, Aryl-, Arylalkyl-, Allyl-, Silyl-, Benzoat- und Pivalat-Teilen; und/oder
(iii) tert-Butyl.

12. Ein Verfahren gemäß Anspruch 10 oder 11, worin die Dichlor-Verbindung von Formel (1) mit dem mono-geschützten Ethylenglykol gekoppelt ist in Gegenwart:

(i) einer Base; und/oder
(ii) einer Base, die aus der Gruppe ausgewählt wird, die besteht aus Alkalimetallhydroxiden, Erdalkalimetallhydroxiden, Natrium-Metallen, DBU, DBN, DMAP und Pyridin; und oder
(iii) eines Alkalimetallhydroxids; und/oder
(iv) von Lithium- oder Natriumhydroxid; und/oder
(v) eines organischen Lösungsmittels; und/oder

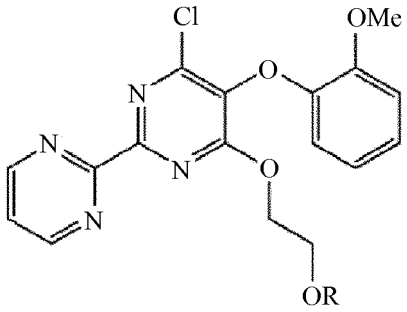
(vi) eines organischen Lösungsmittels, das aus der Gruppe ausgewählt wird, die besteht aus Toluen, THF, Xylen, DMF, DMSO, Acetonitril und Dimethylacetamid; und/oder
(vii) von Toluen.

13. Ein Verfahren gemäß eines der Ansprüche 10-12, worin das Reaktionsgemisch erhitzt wird auf Temperaturen:

(i) zwischen ca. 30-90 °C; und/oder
(ii) zwischen ca. 50-60 °C.

Revendications

1. Un procédé de préparation du bosentan en utilisant un composant de formule (2a) :



(2a)

,

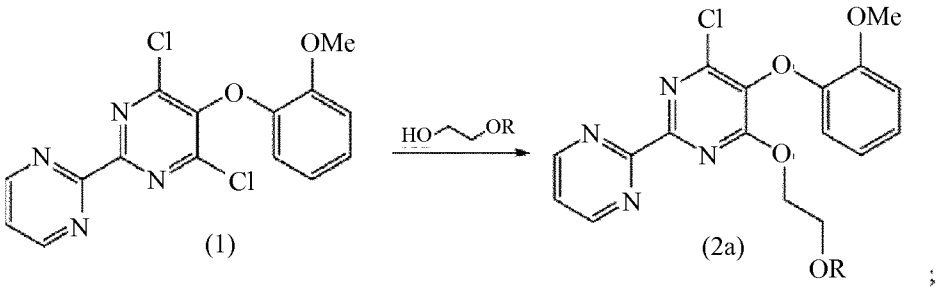
dans lequel R est un hydroxyle protégeant le groupe.

2. Un procédé selon la revendication 1, dans lequel R est :

(i) stable en conditions basiques et légèrement acides ; et/ou
(ii) choisi parmi les groupes alkyle, aryle, arylalkyle, allyle, silyle, benzoate et pivalate ; et/ou
(iii) ter-butyle.

3. Un procédé pour préparer le bosentan comprenant :

(a) la réaction entre un composé dichloré de formule (1) avec un éthylène glycol monoprotégé de formule $HOCH_2CH_2OR$, dans lequel R est un hydroxyle protégeant le groupe, pour donner un composé de formule (2a) :



;

(b) en couplant le composé (2a) avec un 4-ter-butyle phényle sulfonamide ;
(c) en retirant le groupement protecteur R ; et
(d) en isolant le bosentan du mélange obtenu à l'étape (c).

4. Un procédé selon la revendication 3, dans lequel R est :

(i) stable en conditions basiques et légèrement acides ; et/ou
(ii) choisi parmi les groupes alkyle, aryle, arylalkyle, allyle, silyle, benzoate et pivalate ; et/ou

(iii) ter-butyle ; et/ou
(iv) ter-butyle, et dans lequel le groupement ter-butyle est retiré par traitement à l'acide formique suivi d'un traitement à l'hydroxyde de sodium.

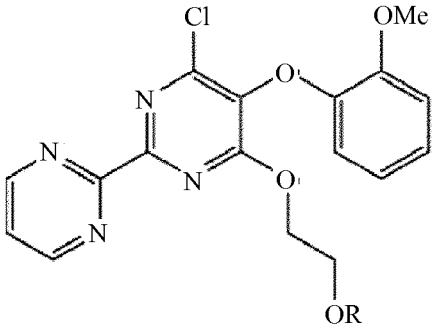
5. Un procédé selon la revendication 3 ou 4, au cours duquel à l'étape (a), le composé dichloré de formule (1) et l'éthylène glycol monoprotégé réagissent en présence de :

(i) une base ; et/ou
(ii) une base choisie dans le groupe comprenant hydroxydes de métaux alcalins, hydroxydes de métaux alcalino-terreux, sodium métallique, DBU, DBN, DMAP et pyridine ; et/ou
(iii) un hydroxyde de métal alcalin ; et/ou
(iv) de l'hydroxyde de lithium ou de sodium ; et/ou
(v) de l'hydroxyde de sodium.

6. Un procédé selon une des revendications 3 à 5, dans lequel :

(i) le procédé s'effectue dans un solvant organique ; et/ou
(ii) l'étape (a) s'effectue dans un solvant organique choisi dans le groupe comprenant le toluène, THF, xylène, DMF, DMSO, acétonitrile et diméthylacétamide ; et/ou
(iii) l'étape (a) s'effectue dans le toluène ; et/ou
(iv) le mélange réactif à l'étape (a) est chauffé à une température comprise entre 30 °C et 90 °C environ ; et/ou
(v) le mélange réactif à l'étape (a) est chauffé à une température comprise entre 50 °C et 60 °C environ ; et/ou
(vi) le bosentan est isolé à l'étape (d) par filtration puis séché sous pression réduite jusqu'à atteindre une masse constante.

7. Un composé présentant la structure indiquée par la formule (2a) ou une forme sel ou cristalline correspondante :



(2a)

,

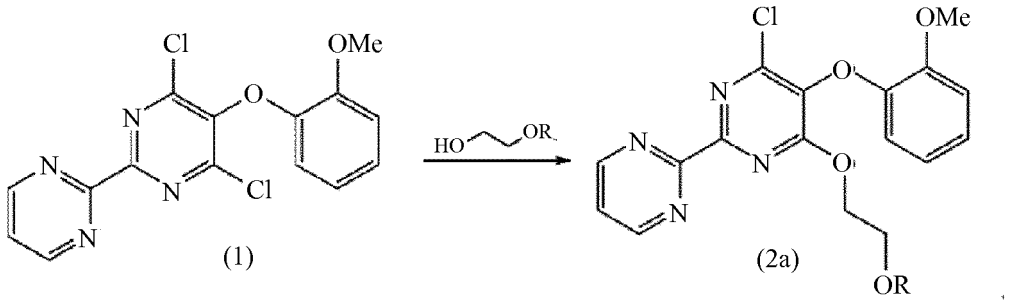
dans lequel R est un hydroxyle protégeant le groupe, choisi parmi les groupes alkyle, alkényle, alkynile, aryle, arylalkyle, arylalkényle, arylalkynyle, alkylaryle, alkénylaryle, alkynylaryle, allyle, silyle, benzoate et pivalate.

8. Un composé selon la revendication 7, dans lequel R est :

(i) choisi parmi les groupes alkyle, aryle, arylalkyle, allyle, silyle, benzoate et pivalate ; et/ou
(ii) ter-butyle.

9. Un composé selon les revendications 7 ou 8, dans lequel le sel est choisi dans le groupe comprenant : un tartrate, succinate, oxalate, pimélate, adipate, acétate, subérate, salicylate, mésylate, malate, malonate, maléate, camphosulfonate, mandélate, chlorhydrate, sulfate d'hydrogène, sulfate, bromhydrate, bésylate, benzoate, dihydrogénophosphate, glutarate, ou sel citrate.

10. Un procédé pour préparer un composé de formule (2a) comprenant le couplage d'un composé dichloré de formule (1) à un éthylène glycol monoprotégé de formule $HOCH_2CH_2OR$, dans lequel R est un hydroxyle protégeant le groupe, pour donner un composé de formule (2a) :



11. Un procédé selon la revendication 10, dans lequel R est

(i) stable en conditions basiques et légèrement acides ; et/ou
(ii) choisi parmi les groupes alkyle, aryle, arylalkyle, allyle, silyle, benzoate et pivalate ; et/ou
(iii) ter-butyle.

12. Un procédé selon la revendication 10 ou 11, au cours duquel le composé dichloré de formule (1) est couplé à l'éthylène glycol monoprotégé en présence de :

(i) une base ; et/ou
(ii) une base choisie dans le groupe comprenant hydroxydes de métaux alcalins, hydroxydes de métaux alcalino-terreux, sodium métallique, DBU, DBN, DMAP et pyridine ; et/ou
(iii) un hydroxyde de métal alcalin ; et/ou
(iv) de l'hydroxyde de lithium ou de sodium ; et/ou
(v) un solvant organique ; et/ou
(vi) un solvant organique choisi dans le groupe comprenant le toluène, THF, xylène, DMF, DMSO, acétonitrile et diméthylacétamide ; et/ou
(vii) du toluène.

13. Un procédé selon une des revendications 10 à 12, au cours duquel le mélange réactif est chauffé :

(i) à une température comprise entre 30 °C et 90 °C environ ; et/ou
(ii) à une température comprise entre 50 °C et 60 °C environ.

REFERENCES CITED IN THE DESCRIPTION

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Patent documents cited in the description

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